REMARKS

Upon entry of the above amendments, Claims 1, 36, 39 and 57 are pending. Claim 57 has been amended to more distinctively claim the subject matter of the invention. No new matter has been added.

Rejections under 35 U.S.C.§ 101

Claims 1, 36, 39 and 57 remain rejected by the Examiner under 35 U.S.C.§101 as the Examiner contends that the claimed invention is not supported by substantial asserted utility or a well established utility. The Examiner has stated that the specification does not show whether the claimed polypeptide is overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control and invited applicants to present data that the claimed protein overexpression is correlated with cancer or any other disease.

Applicants strongly disagree with the Examiner's rejection.

Applicant's assertion of utility

Applicant's response, dated April 7, 2003 to the November 6, 2002 Office Action states:

> "Applicants submit that at least one substantial and specific utility exists for the claimed invention...Applicants assert that the specification identifies and the accompanying 37 C.F.R. § 1.132 declaration (Gerlach Declaration) supports at least one specific and credible utility. The invention as claimed is useful as a marker for identifying cancer cells."

In the July 3, 2003 Office Action the Examiner maintains the rejection asserting that the invention is not supported by a substantial asserted utility or a well established utility.

Applicants respectfully submit that the Examiner's position is improper. Applicants' assertion of utility creates a presumption of utility sufficient to satisfy the utility requirement of 35 U.S.C. §101. As a matter of Patent Office practice, the Applicants' assertion of utility must be taken as sufficient to satisfy the utility requirement of Section 101 unless there is a reason for one skilled in the art to question the objective truth of the statement.

The Examiner argues that Applicants' data does not disclose if protein overexpression is correlated with any cancer or any other disease. Applicant strongly disagrees. Applicant has shown that:

1) NOV1b gene expression is elevated in breast cancer tissue samples from patients and cell lines as well as ovarian, lung, and bladder cancer tissue samples or cell lines (Gerlach Declaration); and
2) In cell lines with elevated gene expression, breast cancer cell lines T47D, MCF7 and ovarian carcinoma cell line OVCAR-3, NOV1b protein is also expressed (Declaration under 37 C.F.R. § 1.132 by Dr. Michael Jeffers (Jeffers Declaration) presented in Applicants' reply dated January 5, 2004).

Applicants have shown that protein expression is correlated with cancer, particularly breast and ovarian carcinomas.

Lack of Prima Facie showing

The Examiner argues that "the art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide." The Examiner cites references regarding a) ferritin, b) transferring receptor, c) ornithine decarboxylase, d) p-glycoprotein, and e) p53 in support of the Examiner's position.

Applicant strongly disagrees. While it is true that the art recognizes a variety of factors that influence the translation of mRNA into polypeptides, basic biology teaches that the genetic code is enacted through translation of DNA into RNA which is spliced to produce mRNA which is translated into protein. (See for example, Protein Synthesis 1999 by Access Excellence @ the national health museum, attached as Appendix A). When mRNA is not translated into protein, it is an exception to the common understanding in the art.

Each reference relied upon by the Examiner is addressed herein below:

a) Ferritin, (Alberts et al. pg 465): The Examiner states:

> "translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation."

Applicants respectfully point out that this reference also specifically states:

> "Steroid hormones, for example, affect a cell not only by increasing the transcription of specific genes, but also by increasing the stability of several of the mRNAs encoded by these genes." (emphasis added)

This reference discusses the stability of mRNA in response to certain factors, in this case, iron levels. Instances of increased transcription and increased stability of mRNA resulting in synthesis of protein would be detectable by mRNA levels present in the cell and nothing in this reference suggests otherwise. The reference also does not specifically address the affect of increased expression of mRNA and does not suggest that increased expression of mRNA would not result in increased protein levels.

b) Transferrin receptor (Alberts): The Examiner states:

> "Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferring receptor polypeptide is translated."

Applicants respectfully point out that if the mRNA is degraded, it would not be detectable, or at least would be detected at lower levels in the cell and similarly little or no polypeptide would be detected. This is not contrary to Applicants' position. Furthermore, the reference states:

> "Here aconitase binds to the 3'UTR of the transferrin receptor mRNA and causes an increase in receptor production, presumably by inhibiting the function of sequences that otherwise cause rapid degradation of the mRNA." (emphasis added)

Inhibition of mRNA degradation would mean increased levels of mRNA which could be detected in the cell, corresponding to increased receptor production. The reference does NOT specifically address protein expression in situations of increased transferrin mRNA. The reference does not teach or suggest that increased levels of transferrin receptor mRNA would not correspond to increased levels of transferrin receptor protein.

c) ornithine decarboxylase (Shantz and Pegg): The Examiner contends:

> "ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of mRNA and the availability of elF-4E, which mediates translation initiation."

Applicants respectfully point out that this reference pertains to ODC and AdoMetDC protein levels being highly regulated in the cell, mostly at the level of translation. The reference states that regulation of quick changes in the amount of enzyme protein

> "can occur at the levels of transcription, translation and protein degradation....For example, the promoters of the genes encoding ODC and AdoMetDC contain multiple regulatory elements, and there are numerous examples of transcriptional regulation of both genes by growth factors, hormones and tumor promoters...Increased levels of mammalian AdoMetDC mRNA, which presumably are due to changes in transcription have been seen in response to growth factors..."" (emphisis added).

Transcriptional regulation of both genes is regulated by i.e. growth factors and increased levels of AdoMetDC mRNA is seen in response to growth factors. While Shantz and Pegg teach a variety of factors influencing enzyme activity, translation rates and efficiency, activation of translation initiation factors, protein synthesis, it is evident that Shantz and Pegg believe that increased mRNA results in increased amounts of enzyme protein. Shantz and Pegg do not specifically teach any findings where increased expression of the gene, did not lead to increased expression of the protein.

d) p-glycoprotein (McClean and Hill): The Examiner contends:

> "p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA."

As the Examiner contends, McClean and Hill do teach of findings where increased protein expression is seen without increased mRNA. However, McClean and Hill do not teach any instance where increased expression of mRNA did not coincide with increased protein levels. Applicants respectfully submit that the reference specifically says:

> "Pgp expression is considered to be regulated by a number of mechanisms, including gene amplification, transcriptional activation and translational or post-translational modifications. For example, Chinese hamster ovary (CHO) cells, selected clonally with increasing concentrations of chochicine, exhibited an increase in Pgp gene copy number, Pgp mRNA and protein, at every step in the selection procedure." (emphasis added)

Increased Pgp mRNA resulted in increased protein in CHO cells.

e) p53 protein (Fu et al): The Examiner states:

> "levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene."

Applicants respectfully point out that the reference pertains to findings of varying levels of p53 protein in spite of p53 mRNA presence. P53 is a tumor suppressor gene and the presence of wild type p53 protein suggests a level of control over tumor proliferation. In some tumors, mutation of p53 leads to lack of control and tumor proliferation. These authors suggest that while p53 mutation rates are low in acute myelogenous leukemia, the protein is not detected in many of the blast samples, possibly explaining the loss of p53 control. Fu et al., teaches that they do detect mRNA levels in the blast samples and seek to explain variable levels, or absence of protein. Underlying the explanation is the understanding that if there is mRNA there should be protein. Fu et al., clearly states:

> "We found control both at the level of RNA abundance and at the level of translation. The level of protein expression measured by metabolic labeling and immunoprecipitation is dependent primarily on the rate of protein synthesis, the rate of protein degradation and the amount of mRNA available for translation." (emphasis added).

Fu et al., does still find the amount of mRNA to be influential on protein present in the samples. Fu et al, do describe a pair of cell lines, OCI/AML-3 and OCI/AML-4 that

appear to have the same level of p53 protein but that have a 4-fold difference in p53 RNA. Fu et al., use this unusual pair of cell lines to further investigate why, counter to standard understanding, this would occur. However, in both cell lines mRNA is present as well as protein. Fu does not address protein levels in cells where p53 mRNA is specifically overexpressed.

Applicants respectfully submit that none of these references would cause one of skill in the art to question the substantial nature of the applicants asserted utility. The majority of the references relied upon by the examiner do not specifically address protein expression in situations of increased mRNA expression. Furthermore, the references are not specific to the Applicants' protein. The references do not even pertain to proteins remotely homologus to the Applicants' protein. At best, the references cited by the examiner do nothing more than merely question operability, i.e. increased mRNA expression (Applicant's evidence) *might not operably correlate* with increased protein expression. However, it is just as possible that increased mRNA expression *would* correlate with increased protein expression. For example, Guy et al 1992 (PNAS, USA 89: 10578-10582, see Appendix B) describes elevated levels of neu mRNA and protein. "In a large percentage of these human samples, overexpression of neu was associated with gene amplification." Additionally, in Applicants' response to the July 3, 2003 Office Action, the Jeffers Declaration provides clear evidence that cells expressing mRNA encoding Applicants' protein SEQ ID NO:4 also express SEQ ID NO:4 protein.

Therefore a prima facie showing that the claimed invention lacks utility has not been established by the Examiner. A prima facie showing must articulate sound reasons why a person of ordinary skill in the art would conclude that it is more likely than not that an asserted utility is not credible. The Examiner has clearly not shown that one of skill in the art would consider Applicants' asserted utility not credible. Even so, the Examiner has maintained the position that the invention is not supported by a substantial asserted utility or well established utility. Assuming arguendo, the Examiner intended to reject the pending claims based upon a lack of credible utility, Applicant respectfully submits that the arguments presented above refute such a rejection and that the Examiner's points do nothing to cause one of skill in the art to question the asserted credible utility.

Correlation of *in vitro* data with *in vivo* data

The Examiner further contends that the Jeffers Declaration providing an *in vitro* demonstration of protein expression in certain cancer cell lines is not found persuasive as "the art recognizes that *in vitro* data do not correlate to *in vivo* data..." The Examiner cites Freshney and Dermer is support of this position.

Applicants strongly disagree. The Examiner contends that:

"Freshney teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*...This has often led to tissue culture being regarded in a rather skeptical light."

The reference is a technique manual on the culture of animal cells and it says that:

> "tissue culture technology has also been adopted into many routine applications in medicine and industry".

Freshney goes on to say:

> "It is clear that the study of cellular activity is tissue culture may have many advantages; but in summarizing these, below, considerable emphasis must also be placed on its limitations, in order to maintain some sense of perspective."

Of the differences between cells *in vitro* and *in vivo* Freshney says:

> "Although the existence of such differences cannot be denied, it must be emphasized that many specialized functions are expressed in culture and as long as the limits of the model are appreciated, it can become a very valuable tool."

Freshney does not teach that *in vitro* data does not correlate with *in vivo* data.

Applicants respectfully submit that Dermer's position is that the search for a cure for cancer has been unsuccessful because of the over reliance on cell lines for study. He suggests that one needs to ask if the model is correct. He suggests that scientists should not look for the exception that proves the rule. He suggests that both normal and malignant should first be identified instead of relying on models that mimic. Applicants respectfully point out that they have done just that in identifying a differentiation of NOV1b expression in malignant versus normal tissue samples from patients (see Gerlach Declaration). Applicant then shows by way of cell lines that cells expressing NOV1b mRNA, express NOV1b protein (see Jeffers Declaration). The correlation of NOV1b with cancer is not totally based upon in vitro cell line data, it includes data from samples from patients.

The Examiner concludes that:

"based on the cell culture data presented in the declaration, it could not be predicted that either SEQ ID NO;4 or its fragment could be overexpressed in vivo cancers.... Therefore the disclosed utilities are not considered specific, credible and substantial because they are just invitations for one skilled in the art to figure out how the protein functions or what the biological activities are for the invention."

Applicants again must express strong disagreement with the Examiner's position. To disregard the Applicants' declaration and persist in the rejection, the Examiner must articulate sound reasons why a person of skill in the art would conclude that it is more likely than not that to be true. The Examiner has provided 1) a cautionary statement by Freshney that cell culture results must be considered from the appropriate perspective and 2) Dermer's personal view that drug discovery research based on cell lines will not cure cancer. Neither reference would persuade one of skill in the art to disregard Applicants' data. While the Examiner contends that it could not be predicted that the Applicant's invention could be expressed in *in vivo* cancers, nothing has been presented that proves that the Applicants' invention could not be expressed in *in vivo* cancers.

Furthermore, Applicants respectfully submit that the standard in the art is frequently to use in vitro methods such as cell lines, prior to proceeding to *in vivo* experiments. In 1985 the National Cancer Institute changed its drug screening program from an *in vivo* screen to an *in vitro* screen of tumor cell lines, which later was followed up with secondary screens in tumor xenografts from the cultured cell lines. (Boyd MR, In Teicher BA, ed. Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval. Humana Press, Totowa, NJ, 1997; pp.23-42 see Appendix C; Plowman J et al, In Teicher BA, ed. Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval. Humana Press, Totowa, NJ, 1997; pp.101-125 see Appendix D) Standard research has also focused increasingly on target validation or "credentialing" Wittes and Klausner which begins at the cellular level, moves through tumor models in animals and culminates in translation to the clinic(as reviewed by Harrison S, In Teicher BA, ed. Tumor Models in Cancer Research. Humana Press, Totowa, NJ, 2002; pp.3-19 see Appendix E). Kelland et al (1989 Radiotherapy & Oncology 16:55-63, see Appendix F) reported that the comparision of the *in vitro* and *in vivo* radiation response for 3

cervical carcinoma cell lines and corresponding xenografts showed a general tendency for the *in vivo* results to follow that predicted by the *in vitro* studies. Another study demonstrated that in 8 paired ovarian cancer cell lines and xenografts, and reported a highly statistically significant positive correlation for *in vitro* sensitivity versus *in vivo* responsiveness to cisplatin and carboplatin (Kelland et al 1992, Cancer Chemother Pharmacol 30:43-50 see Appendix G). The NCI compared activity in xenografts versus a cell line hollow fibre assay and *in vitro* cell line assays. There was a strong correlation between potency in the cell line screen and activity in the hollow fibre assay and increased activity in the hollow fibre assay predicted for increased xenograft activity (Johnson JI et al., 2001 British Journal of Cancer 84:1424-1431 see Appendix H).

In summary it is quite clear that one of skill in the art would not make the determination that *in vitro* data does not correlate with *in vivo* data. Therefore it is improper for the Examiner to dismiss Applicants' *in vitro* data as not persuasive, not relevant to *in vivo* conditions, or not "germane to the rejection at issue". Furthermore as a matter of patent office practice it is improper for the Examiner to persist in the rejection of the claims under 35 U.S.C. §101 as not supported by a substantial asserted utility or well established utility when a prima facie showing can not be made.

Improper to request *in vivo* data

In the Office Action dated July 3, 2003, the Examiner invited the Applicants to "present evidence that the protein over-expression is correlated with in vivo cancer or any other diseases to obviate" the 35 U.S.C. §101 rejection. Applicants respectfully submit that it is not proper as a matter of law for the Examiner to require correlation of protein overexpression with *in vivo* cancer.

First, the Applicants have asserted a specific, substantial and credible utility for the claimed invention. The Examiner has not presented any support why Applicants' evidence for asserted utility would not be considered persuasive to one of skill in the art. None of the documents that were cited by Examiner support any factual basis for the Examiner's finding. The Examiner has not established a prima facie showing that the claimed invention lacks utility.

Second, Applicants have presented evidence for mRNA expression in samples of cancerous tissue obtained from patients. Applicants then presented evidence that mRNA in cells is translated into protein. One of skill in the art would conclude that it is more likely than not that the mRNA in the cancer samples (as compared to cell lines) is translated into protein. The Examiner has not established a prima facie showing that the claimed invention lacks utility.

Third, an invitation to substantiate an asserted utility for a claimed invention was supported in In re Citron, where the court held that when an "alleged utility appears to be incredible in the light of the knowledge of the art, or factually misleading, applicant must establish the asserted utility by acceptable proof" (325 F.2d at 253, 139 USPQ at 520 (CCPA 1963). However, in the present case, the Examiner has not established that the Applicants' asserted utility is incredible, inoperative or misleading. Furthermore, the Examiner's request is not proper in view of In re Brana (51 F.3d 1560, 34 USPQ2d 1436, Fed. Cir. 1995).

Applicants respectfully submit that the Examiner's request is not proper and unnecessary to substantiate the asserted utility of the present invention. However, in the interests of advancing the prosecution of this application, Applicants present herewith a Declaration under 37 C.F.R. § 1.132 of Dr. John MacDougall which clearly demonstrates increased levels of the NOV1b protein (CG55343) in breast and lung adenocarcinoma tumor samples from patients, as compared to normal human breast and lung tissue.

Applicants respectfully submit that a prima facie showing that the claimed invention lacks utility has not been established by the examiner. Furthermore, Applicants have presented exhaustive evidence in support of utility. Applicants therefore respectfully request the rejection under 35 U.S.C. §101 be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1, 36, 39 and 57 were rejected under 35 U.S.C. §112, first paragraph, as the examiner states that since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicant disagrees and submits that there is a credible,

specific and substantial asserted utility for claimed polypeptide SEQ ID NO:4 as stated above and that the 35 U.S.C. §101 rejection has been overcome, therefore the 35 U.S.C. §112 rejection has been overcome and should be withdrawn.

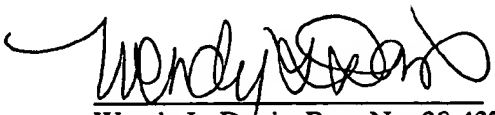
Claim 57 is rejected under 35 U.S.C. §112, first paragraph as the Examiner alleges that the claim fails to comply with the written description requirement. Applicant strongly disagrees. The Examiner's attention is respectfully invited to the specification, page 10, lines 5-7 which state: "The NOV1b protein was analyzed for signal peptide prediction and cellular localization. SignalP results predict that NOV1b is cleaved between position 38 and 39 of SEQ ID NO:4, i.e. at the slash in the amino acid sequence TVT-IF." Furthermore the current specification states: "The product "mature" form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps as they may take place within the cell, or host cell, in which the gene product arises. Examples of such processing steps leading to a "mature" form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an ORF, or the proteolytic cleavage of a signal peptide or leader sequence." (See page 98, lines 19-23) One of skill in the art appreciates that the signal peptide directs the protein during synthesis to particular cellular compartments where the protein is completed. The signal peptide is cleaved resulting in the final, finished or "mature" protein. Hence, as clearly supported in the specification, the NOV1b mature protein sequence is the amino acid sequence SEQ ID NO:4 minus the 1-38 signal peptide, i.e. amino acids 39-313 of SEQ ID NO:4.

To advance prosecution of this application, Applicant has amended claim 57 herein to more distinctively point out what Applicant considers is the current invention. Applicant reserves the right to prosecute the subject matter of the claim as originally presented in subsequent applications. "Whatever is now claimed" (Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111) is clearly described in the application as filed. One of skill in the art can certainly envision the detailed chemical structure of the encompassed polypeptide as amino acids 39-313 of SEQ ID NO:4. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Applicants respectfully submit that this paper is fully responsive and that the pending claims are in condition for allowance. Such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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